Claims 1 and 2 stand rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent 5,543,428. Transmitted herewith is a terminal disclaimer under 37 C.F.R. § 1.321(b), disclaiming any term beyond the expiration date of U.S. Patent No. 5,543,428 and stating the signatory's interest in the application. Withdrawal of the obviousness-type double patenting rejection is respectfully requested.

Claims 1 and 2 stand rejected under 35 U.S.C. § 112, paragraph 1, for lack of enablement. The Examiner indicates that the specification is enabling for the specific multidrug-resistant neoplasm disclosed, but does not reasonably provide enablement for the term "multidrug resistant neoplasm." Claim 1, and dependent claim 2, have been amended to specify a method of treating a patient having a multidrug-resistant neoplasm "having a pathway for resistance including the multidrug-resistance protein MRP." Accordingly, claim 1, and dependent claim 2, as amended, are directed to the specific multidrug resistant neoplasm disclosed.

There are two forms of multidrug resistance proteins described in the specification of the captioned application. As stated on page 2, lines 10-12 of the specification, "[o]ne form of multi-drug resistance (MDR) is mediated by a 170-180 kD energy-dependent efflux pump designated as P-glycoprotein, p-gp." Thus, one form of multidrug resistance protein described in the specification is P-glycoprotein, a 170-180 kD protein. The other form of multidrug resistance protein described in the specification is a 190 kD protein that is not P-glycoprotein, and is designated MRP (see page 2, lines 22-24). As stated on page 2, lines 26-28 of the specification "[p]190, *also referred to as MRP*, is found on the plasma membrane and also appears to be localized in the endoplasmic reticulum."

B

(emphasis added). Therefore, the 190 kD form of the multidrug resistance protein is designated in the specification of the captioned application as "MRP."

The Examiner concedes that the specification of the captioned application is enabling for the specific multidrug resistance protein MRP disclosed in the specification (see page 2, paragraph 5 of Paper No. 8). It is clear, too, that the specific multidrug resistance protein disclosed in the instant specification, the 190 kD protein referred to as MRP, is enabled. The capacity of leukotrienes to inhibit the activity of the multidrug resistance protein was tested in the present application in HL60/ADR cells which is a cell line that has developed multidrug resistance. As shown in Example 21 (pages 69-70), a 190 kD protein was detected by photoaffinity labeling with radiolabeled leukotriene C_4 in HL60/ADR membranes, whereas only a slight labeling was detected in membranes from revertant and parental cells not exhibiting multidrug resistance. Thus, the presently claimed leukotriene-related compounds bind to the 190 kD MRP protein indicating that the claimed compounds act by inhibiting the activity of this specific multidrug resistance protein. For the foregoing reasons, the specification enables the 190 kD multidrug resistance protein as being the form of the multidrug resistance protein inhibited by the claimed compounds. Withdrawal of the rejection of claims 1 and 2 under 35 U.S.C. § 112, paragraph 1, is respectfully requested.

Claims 1 and 2 stand rejected under 35 U.S.C. § 112, paragraph 2, for indefiniteness. The Examiner indicates that the addition of the phrase "to said patient" after the term "administering" in claim 1 will overcome the rejection. Claim 1, and dependent claim 2, have been amended to add the phrase "to said patient" after the term "administering." Withdrawal of the rejection of claims 1 and 2 under 35 U.S.C. § 112, paragraph 2, is respectfully requested.

CONCLUSION

The claim amendments and remarks presented herein are believed to address fully each of the Examiner's rejections. Applicants respectfully request allowance of the pending claims and passage of the application to issuance.

Respectfully submitted,

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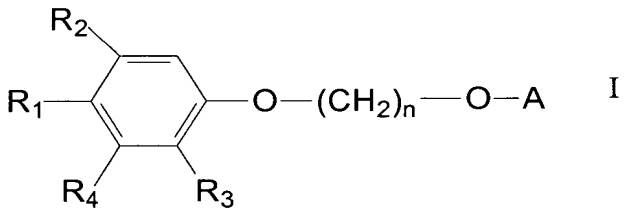
6

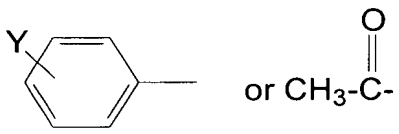
Appendix to Amendment
Marked-Up Version of Rewritten Claims Under 37 C.F.R. § 1.121(c)(1)(ii)
Application No. 09/836,567

1. A method of treating a patient having a multidrug-resistant neoplasm having a pathway for resistance including the multidrug-resistance protein MRP, said method comprising the step of inhibiting membrane transport mediated by the [multidrug resistance] multidrug-resistance protein MRP by administering to said patient an effective amount of a compound of Formula I



I

wherein R_1 is



Y is hydrogen or halo;

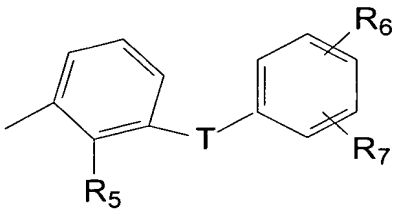
R_2 is hydrogen, -OH, or -OCH_3;

R_3 is C_1-C_6 alkyl;

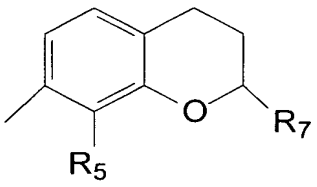
R_4 is hydrogen, -OH, or -OCH_3;

n is 3, 4, or 5;

A is



or



R_5 is hydrogen, C_1-C_6 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, or phenyl;

R_6 is hydrogen or halo;

R_7 is -COOH or 5-tetrazolyl;

T is a bond, $-CH_2-$, -O-, -C(=O)-, or $-S(O)_q-$; and

q is 0, 1, or 2;

provided when one of R_2 and R_4 is -OH or $-OCH_3$, the other of R_2 and R_4 must be hydrogen,

or a pharmaceutically acceptable base addition salt or solvate thereof.